

# Comparison of two different protocols for the early assessment of disease free status in the follow-up of patients with low risk papillary thyroid carcinoma

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## Summary

Our previous protocol for the follow-up and treatment of patients with differentiated thyroid carcinoma (DTC), used until December 2000, consisted in performing the already classical diagnostic whole body scans (Dx WBS) using 10 mCi of <sup>131</sup>I in association with the assessment of a stimulated serum thyroglobulin (Tg). When the patient had two consecutive negative Dx WBS, associated with an undetectable stimulated Tg level, we considered that such individual reached the disease free (DF) status. Due to the poor results observed with this traditional protocol, we have designed a new one.

**Objective:** The aim of our study was to compare the results of this new proposed protocol (Group 1) with the old one (Group 2).

**Design:** The new protocol consisted, on one hand, in not performing the Dx WBS, previous to an ablative or therapeutic radioiodine dose, but always performing the post-dose WBS (PD WBS) one week after the administration of the <sup>131</sup>I dose. By the other hand, the DF status was defined when one PD WBS was negative together with an undetectable stimulated Tg, in presence of negative Tg Ab.

**Subjects and Methods:** The first DF fifteen patients included within the new protocol (Group 1) and the last DF fifteen patients evaluated with the old protocol (Group 2) were compared. No statistically significant differences were found when age, gender and TNM stages were compared between groups.

**Results:** The cumulative radioiodine activity to reach the DF status was significantly higher in Group 2 ( $338 \pm 123$  mCi) as compared with that received in Group 1 ( $268 \pm 94$  mCi);  $p < 0.0039$  between groups. The mean time to define the DF status was  $17 \pm 9$  months in Group 1 vs.  $43 \pm 19$  months in Group 2 ( $p < 0.002$ ). Patients in Group 2 had to withdraw thyroid hormone replacement (hypothyroid state)  $5.3 \pm 2.1$  times in their follow-up to define the DF status, while in Group 1, only  $2 \pm 1$  hypothyroid states were enough to define this status ( $p < 0.004$ ). The time during which patients had to suffer the hypothyroid state were  $8.5 \pm 4.2$  weeks in Group 1 vs.  $22.4 \pm 12$  weeks in Group 2 ( $p < 0.001$ ).

In conclusion, our new protocol allowed for an earlier definition of the DF status of DTC. Most probably, the previous use of Dx WBS contributed, due to the thyroid cell «stunning», to have a lesser efficacy of the ablative/or therapeutic radioiodine doses. The fact of considering the PD WBS as the most important tool in association with stimulated Tg measurement, also avoids the errors of having false negative scans when using the smaller doses of the Dx WBS. This new protocol also improved the quality of life of our patients, determined by a lesser exposure to the severe hypothyroid state.

**Key words:** Thyroid, cancer, carcinoma, follow-up, radioiodine dose

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## Resumen

### Compensación entre dos protocolos diferentes para llegar más precozmente al estado libre de enfermedad en el seguimiento de pacientes con carcinoma papilar de tiroides de bajo riesgo

Nuestro protocolo previo para el seguimiento y tratamiento de pacientes con carcinoma diferenciado de tiroides (CDT) usado hasta diciembre de 2000, consistía en realizar el clásico rastreo corporal total diagnóstico (RCT Dx) usando 10 mCi de  $^{131}\text{I}$  en asociación con la medición del nivel de tiroglobulina (Tg) estimulada. Cuando el paciente presentaba dos RCT Dx negativos consecutivos asociados con un nivel indetectable de Tg estimulada, era considerado libre de enfermedad (LE). Debido a los pobres resultados observados con este protocolo tradicional, designamos uno nuevo.

**Objetivo:** El propósito de nuestro estudio fue comparar los resultados de este Nuevo protocolo propuesto (Grupo 1) con los observados con la manera antigua de seguimiento.

**Diseño:** El nuevo protocolo consistía, por un lado, en no realizar el RCT Dx antes de una dosis ablativa o terapéutica de radioyodo pero siempre realizar el RCT post dosis (RCT PD) una semana después de la administración de la dosis de  $^{131}\text{I}$ .

Por otro lado, el estado LE se definió cuando un RCT PD era negativo conjuntamente con un nivel estimulado de Tg indetectable, en presencia de ATG negativos.

**Sujetos y Métodos:** Se compararon los primeros quince pacientes LE incluidos en el nuevo protocolo (Grupo 1) y los últimos quince pacientes considerados LE con el protocolo antiguo (Grupo 2). No se encontraron diferencias estadísticamente significativas cuando se comparó edad, sexo y estadio TNM entre los grupos.

**Resultados:** La dosis acumulada de radioyodo para alcanzar el estado LE fue significativamente mayor en el Grupo 2 ( $338 \pm 123$  mCi) comparada con la que recibieron en el Grupo 1 ( $268 \pm 94$  mCi);  $p < 0.0039$  entre los grupos. El tiempo promedio para definir el estado LE fue de  $17 \pm 9$  meses en el Grupo 1 vs.  $43 \pm 19$  meses en el Grupo 2 ( $p < 0.002$ ). Los pacientes del Grupo 2 tuvieron que suspender la terapia de reemplazo hormonal (estado hipotiroideo)  $5.3 \pm 2.1$  veces en su seguimiento para definir el estado LE, mientras que en el Grupo 1, solo  $2 \pm 1$  estados hipotiroideos fueron suficientes para definirlo ( $p < 0.004$ ). El tiempo durante el cual los pacientes tuvieron que sufrir el estado hipotiroideo severo fue de  $8.5 \pm 4.2$  semanas en el Grupo 1 vs.  $22.4 \pm 12$  semanas en el Grupo 2 ( $p < 0.001$ ).

En conclusión, este nuevo protocolo nos permitió una definición más temprana del estado LE. Probablemente, el uso previo de los RCT Dx contribuyó, debido al «atontamiento» tiroideo, a una menor eficacia de las dosis ablativas o terapéuticas. El hecho de considerar el RCT PD en asociación con el nivel estimulado de Tg como las herramientas más importantes evita, además, los errores de presentar RCT Dx negativos. Por otra parte, este nuevo protocolo mejoró la calidad de vida de nuestros pacientes, determinada por una menor exposición al estado hipotiroideo severo.

**Palabras clave:** tiroides, cáncer, carcinoma, seguimiento, dosis, radioyodo

## Introduction

Differentiated thyroid carcinoma has an excellent prognosis after the initial treatment, which usually includes near-total thyroidectomy and radioiodine ablation of post-surgical thyroid remnants<sup>1</sup>.

In order to administer a radioiodine dose it is necessary to obtain an adequate  $^{131}\text{I}$  uptake in the target tissue focus. For this aim, the suppressive therapy with thyroid hormone must be withdrawn during several weeks, to raise endogenous TSH to levels associated with increased iodine uptake by thyroid tissue (usually greater than 25 mUI/L)<sup>2,3</sup>.

When total or near-total thyroidectomy seems to have successfully removed all malignant

thyroid tissue, some  $^{131}\text{I}$  uptake usually remains in the thyroid bed<sup>4</sup>. The  $^{131}\text{I}$  destruction of this residual macroscopically normal thyroid tissue is referred to as thyroid remnant ablation.

There are three approaches to  $^{131}\text{I}$  therapy: empiric fixed doses, upper bound limits that are set by blood and whole-body dosimetry, and quantitative tumor dosimetry<sup>5</sup>.

Empiric fixed dose is the most widely used and the simplest method. Its main advantages are simplicity and safety. This is the usual method we employ in Argentina.

The use of diagnostic whole body scan (Dx WBS) has been discussed in the last years<sup>4, 6-9</sup>. It is well known that the radioiodine diagnostic dose must be higher to determine the localization of

thyroid tissue, but smaller to avoid thyroid «stunning». By administering more than 2 mCi  $^{131}\text{I}$ , it may have a sufficiently harmful effect on the tissue in which it concentrates, interfering with subsequent uptake of  $^{131}\text{I}$  for several weeks<sup>6,10-11</sup>. By using 2 or 3 mCi  $^{131}\text{I}$  or 500  $\mu\text{Ci}$   $^{123}\text{I}$  may avoid stunning but is less sensitive than larger  $^{131}\text{I}$  doses in identifying remnants or metastases<sup>10,12</sup>.

In this study we present a comparison of two different protocols of following-up with thyroid cancer patients.

### Subjects and Methods

The objective of our study was to compare the results of a new proposed protocol for the follow-up of patients with low risk papillary thyroid carcinoma (PTC) (Group 1) compared with the follow-up and treatment protocol previously employed (Group 2).

Primary criteria included the time (in months) in which we defined the patient as disease free (Group 1 vs. Group 2). Secondary criteria included: a) the number of times of thyroid hormone withdrawal to define the disease free (DF) status between groups; and b) the number of weeks of hypothyroidism suffered by patients in each group. We also considered the presence of one or more severe adverse effects to the radioiodine doses.

### Subjects

To be included in this study, all patients were required to have had the diagnosis of a low risk (Table 1) papillary thyroid cancer (PTC) and have received a total thyroidectomy as surgical approach.

In the prospective protocol (Group 1), we included the first fifteen low risk PTC patients considered as DF. These patients had attended the Endocrine Division of the Hospital de Clínicas and were treated at the Nuclear Medicine Center (CNEA-UBA) after January 2001 and were followed-up at least for 5 year after initial treatment. All subjects in the prospective protocol (Group 1) gave written voluntary consent to participate in the study.

On the other hand, the last fifteen low risk PTC patients considered as DF with the old protocol were included (Group 2).

No statistically significant differences were

found when age, gender, frequency of lymph node metastasis at diagnosis, and TNM stages were compared between groups (Table 2). Mean time of follow-up was  $68,5 \pm 12,45$  months in Group 1 vs.  $64 \pm 11$  in Group 2 ( $p=\text{NS}$ ).

### Methods

Group 1: The first 15 patients considered as DF with the new protocol were included. These patients did not receive a Dx WBS in any time of their follow-up. Approximately, one month after total thyroidectomy, the patient received the empiric fixed radioiodine ablative dose (between 100 to 150 mCi  $^{131}\text{I}$ ). Five to seven days after the administration of the therapeutic dose, a post dose WBS (PD WBS) was performed.

The result of the PD WBS defined the next step in the treatment six months after ablation. Those patients with low risk PTC (Table 2) would receive a new empiric radioiodine dose of 30 mCi. The negative PD WBS after this  $^{131}\text{I}$  dose combined with an undetectable stimulated Tg level, would define our patient as DF and the follow-up would be done only with measurement of Tg/Tg-Ab under L-T<sub>4</sub> therapy and neck ultrasonography every six months.

If the PD WBS after the first radioiodine dose showed metastatic uptake (associated with elevated Tg levels), in the next withdrawal, a new radioiodine dose higher than 100 mCi, without performing a previous Dx WBS, would be administered every 6 to 12 months, until the disease was controlled or until the appearance of adverse events due to radioiodine.

Group 2: The last fifteen patients considered as disease free evaluated with the old protocol, were included. All patients had received Dx WBS with 10 mCi  $^{131}\text{I}$  in their follow-up.

Previous follow-up protocol was as follows: four weeks after total thyroidectomy, each patient received a diagnostic WBS, 48 hours after the administration of 10 mCi  $^{131}\text{I}$  to establish the thyroid remnant size. Two days after this WBS, the patient received an empiric fixed radioiodine dose (between 100 to 150 mCi, depending on the presence of lymph node metastasis) for remnant ablation. Nearly 6 months after ablation, thyroid hormone was withdrawn during the period of about 4 weeks and a new Dx WBS using 10 mCi  $^{131}\text{I}$  and a

measurement of stimulated Tg levels were performed. According to these results, we defined the necessity for a new radioiodine dose.

Before year 2001, two negative Dx WBS associated with an undetectable stimulated Tg level defined our patient as DF.

Table 1. Definition of low risk papillary thyroid cancer

1. Tumor less than 2 cm in diameter
2. Tumor completely removed by surgery
3. With or without lymph node metastasis but without distant metastasis\*
4. Post radioiodine dose WBS showing only thyroid bed uptake
5. Undetectable Tg levels under thyroid hormone suppressive therapy in the short term follow-up (6 months after initial treatment)

\* If lymph node metastasis were present, they should have been completely removed during surgery.

Table 2. Clinical characteristics in 30 patients with papillary thyroid carcinoma included in the study. Group 1 (new protocol), Group 2 (previous protocol) F: Female, M: Male

	Group 1 (n=15)	Group 2 (n=15)	p
<b>Age (years)</b> (X±SD)	45,5 ± 7,1	46,45 ± 7,4	NS
<b>Sex</b> (F/M)	14/1	13/2	NS
<b>Stage</b>			
I	13 (87%)	14 (93%)	NS
II	2 (13%)	1 (7%)	

### Statistical Analysis

Results were expressed as means ± SD. Statistical analysis was performed by Statistica 5.5 for Windows® (Stat Soft Inc., Tulsa, OK, USA). Comparisons between-groups were made by using Student's t-test for independent samples of cases of normal distribution. The CHI-square test was used for nominal variables. Other tests used were Kruskal Wallis ANOVA. The p values are given for these analyses. The level of significance was set at 0.05.

### Results

The cumulative radioiodine activity to reach the DF status was significantly higher in Group 2 (338 ± 123 mCi) as compared with that received in Group 1 (268 ± 94 mCi);  $p < 0.0039$  between groups (Figure 1).

The mean time to define the DF status was 17 ± 9 months in Group 1 vs. 43 ± 19 months in Group 2 ( $p < 0.002$ ) (Figure 2). Patients in Group 2

had to withdraw thyroid hormone replacement (hypothyroid state) 5.3 ± 2.1 times in their follow-up to define the DF status, while in Group 1, only 2 ± 1 hypothyroid states were enough to define this status ( $p < 0.004$ ) (Figure 3). The time during which patients had to suffer the hypothyroid state were 8.5 ± 4.2 weeks in Group 1 vs. 22.4 ± 12 weeks in Group 2 ( $p < 0.001$ ) (Figure 4).

No adverse events were detected after radioiodine dose administration in any patient.

### Discussion

Levothyroxine withdrawal may be associated with severe hypothyroid signs and symptoms, which usually are poorly tolerated<sup>13</sup>. A recently published paper evaluated the consequences of hypothyroidism in DTC patients and concluded that hypothyroidism secondary to withdrawal causes important morbidity, safety risks, and productivity impairment<sup>14</sup>. Additio-

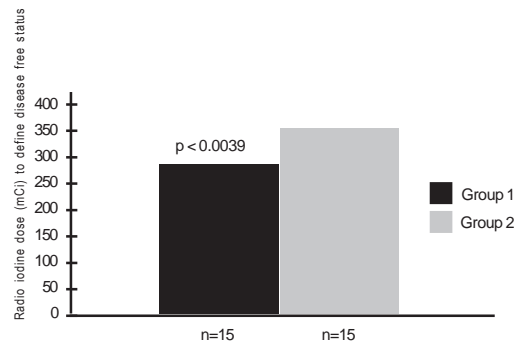
nally, patients who have to pass through several hypothyroid states show a lower compliance with follow-up<sup>15</sup>.

In our study, those patients who received the new protocol (Group 1), had to pass through a lower mean number of hypothyroid states to define the disease free status than those patients in Group 2, thereby arriving earlier to the DF diagnosis. This situation could help PTC patients to comply better with follow-up, avoiding the intolerance generated by numerous severe hypothyroid states when recombinant human TSH can not be used due to economic reasons.

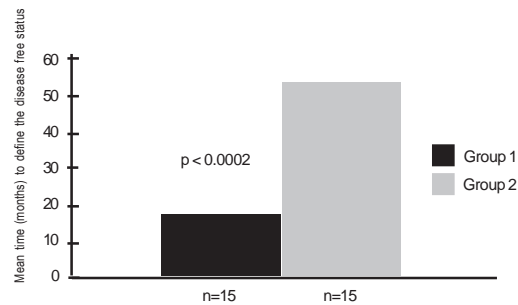
On the other hand, the therapeutic efficacy of <sup>131</sup>I is related to the capacity of the tumor for concentrating and retaining iodine. Half to two thirds of metastases concentrate <sup>131</sup>I, but even after meticulous preparation and large amounts of <sup>131</sup>I the others may not concentrate or retain enough <sup>131</sup>I to achieve a therapeutic benefit<sup>16-18</sup>. This is more common after age 40 and with Hürthle cell cancers<sup>18</sup>. Sodium-iodide symporter (hNIS) expression is low in some thyroid cancers, especially of high tumor stage<sup>19,20</sup>, and posttranscriptional events may cause hNIS dysfunction in others<sup>21</sup>.

The "thyroid stunning" was described for the first time in 1951 by Rawson et al.<sup>4</sup> who concluded that the <sup>131</sup>I radioiodine doses which could not determine tumor destruction might decrease the neoplastic thyroid cells capacity for concentrating the following radioiodine dose. Park et al.<sup>6</sup> found that a diagnostic radioiodine dose of 3 to 10 mCi impaired the uptake of the ensuing thyroablative dose of <sup>131</sup>I in 20 of 26 patients with DTC. Jeevranram et al.<sup>7</sup> showed that 2-3 mCi diagnostic radioiodine dose decreased the thyroid cancer cell uptake of a following <sup>131</sup>I therapeutic dose in 37,48% ( $\pm$  21,24%) in 15 DTC patients.

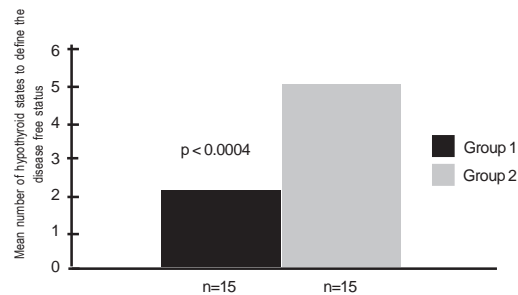
Several other studies have concluded, considering that thyroid tumors may uptake around 0,05-0,5% per gram, that higher radioiodine doses would allow a better observation of potentially treatable lesions<sup>8,9</sup>. It is clear that 10 <sup>131</sup>I mCi allow a better identification of thyroid tissue than 2 mCi, and that 30 mCi might show thyroid cancer metastasis with more accuracy than 10 mCi. Waxman et al.<sup>9</sup> consider that a radioiodine



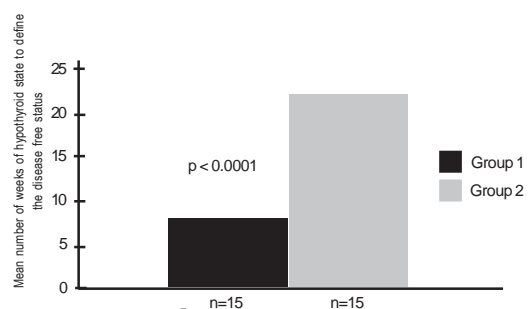
**Figure 1.** Mean <sup>131</sup>I dose administered (mCi) to define the disease free status in 15 patients of Group 1 compared with that received in 15 patients in Group 2.



**Figure 2.** Mean time (in months) necessary to define the disease free status in Group 1 vs. Group 2.



**Figure 3.** Mean number of hypothyroid states necessary to define the disease free status in patients with differentiated thyroid carcinoma from Group 1 and Group 2.



**Figure 4.** Mean time (in weeks) of hypothyroid states necessary to define the disease free status in patients with differentiated thyroid cancer from Group 1 and Group 2.

dose lower than 2 mCi would be inadequate for the follow-up of DTC patients.

The 30 mCi <sup>131</sup>I, used as a second radioiodine dose in those patients with low risk thyroid cancer, would combine efficiently the diagnostic and therapeutic properties. On one side, they would be useful for the identification of pathologic or normal thyroid tissue, and also, might serve to ablate normal thyroid remnants that could have persisted after the post surgical ablative radioiodine dose<sup>22</sup>.

On the other side, the administration of an empiric therapeutic radioiodine dose in those patients with metastatic disease, would allow us to determine the capacity of radioiodine uptake of the metastatic site, in a direct way, and might help to avoid a false negative result after a diagnostic <sup>131</sup>I dose.

On the basis of data from recent studies, <sup>131</sup>I therapy should be individualized according to clinical characteristics. More significantly, in a recent review<sup>23</sup> a decrease in Tg levels was achieved in 63% of DTC patients with detectable Tg levels and negative Dx WBSs, suggesting that <sup>131</sup>I therapy does have a therapeutic effect when the Tg level is considered an index of tumor burden. The 62% positive post-therapy whole-body scanning results in this review of the literature also indicated that a therapeutic dose of <sup>131</sup>I could reveal approximately one half of previously undiagnosed lesions in some patients.

In conclusion, our new proposed protocol allowed for an earlier definition of the disease status of DTC patients as compared with the time needed by using the previous protocol. It also improved the quality of life of our patients, determined by a lesser exposure to the severe hypothyroid state.

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